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(54) **alpha-Aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)benzeneacetonitriles.**

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FR-A-2 231 378
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JOURNAL OF MEDICINAL CHEMISTRY, vol. 26, 1983, pages 96-100, American Chemical Society, Washington, US; R.D. CARROLL et al.: "Anticoccidial derivatives of 6-azauracil. 5. Potentiation by benzophenone side chains"

The file contains technical information submitted after the application was filed and not included in this specification

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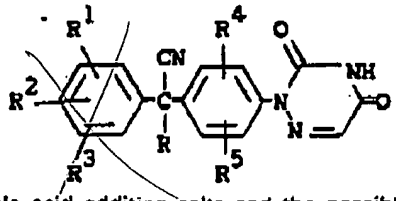
Description

2-Phenyl-as-triazine-3,5-(2*H*,4*H*) diones and their use for controlling coccidiosis have been described in U.S. Patent No. 3,912,723. The phenyl moiety in the said triazines may, inter alia, be substituted with a benzoyl-, a α-hydroxy-phenylmethyl- and a phenylsulfonyl radical.

J. Med. Chem. 1983, *26*, 96—100 similarly describes a series of 2-phenyl-triazine-3,5-(2*H*,4*H*) diones possessing coccidiostatic activity.

The 2-phenyl-as-triazine-3,5-(2*H*,4*H*)diones, described in the present application, differ from the hereinabove-mentioned triazinones, by the substitution of the phenyl moiety with a α-cyano-phenylmethyl radical, resulting in triazine-3,5-(2*H*,4*H*)diones which are very effective in destructing or preventing the growth of *Protozoa* in subjects suffering from such *Protozoa*.

The present invention is related with α-aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitriles having the formula



(I)

the pharmaceutically acceptable acid addition salts and the possible stereochemically isomeric forms thereof, wherein:

R^1, R^2 and R^3 are each independently hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio or C_{1-6} alkylsulfonyl;

R^4 and R^5 are each independently hydrogen, halo, trifluoromethyl or C_{1-6} alkyl; and

R is hydrogen, C_{1-6} alkyl, cyclo C_{3-6} alkyl or phenyl optionally substituted with up to three substituents each independently selected from the group consisting of halo, trifluoromethyl, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio and C_{1-6} alkylsulfonyloxy.

In the foregoing definitions the term "halo" is generic to fluoro, chloro, bromo and iodo; "C_{1-6} alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, butyl, pentyl, hexyl, and the like; "cyclo C_{3-6} alkyl" embraces cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

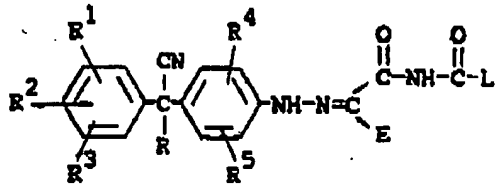
Preferred compounds within the invention are those wherein R^1 and R^2 are, each independently, hydrogen, halo, CF_3, or C_{1-} alkyl; R^3 is hydrogen; R is hydrogen, C_{1-6} alkyl, phenyl or halophenyl; R^4 and R^5 are, each independently, hydrogen, halo, CF_3 or C_{1-6} alkyl.

More preferred compounds within the invention are those wherein R^1 is halo; R^2 and R^3 are both hydrogen; R is hydrogen, C_{1-6} alkyl or halophenyl; and R^4 and R^5 are as described hereinabove for the preferred compounds.

Particularly preferred compounds within the invention are those wherein R^1 is 4-halo, R^2 and R^3 are both hydrogen, R is hydrogen or methyl and R^4 and R^5 are each independently hydrogen, halo, methyl or trifluoromethyl, said R^4 and R^5 are being substituted on the 2 and/or 6 position of the phenyl moiety bearing said R^4 and R^5.

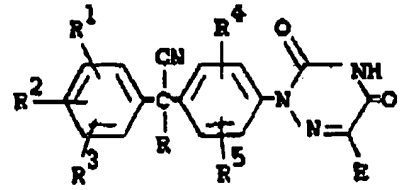
The most preferred compounds of the present invention are selected from the group consisting of 2-chloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrile and 2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)benzeneacetonitrile, the pharmaceutically acceptable acid-addition salts and possible stereochemically isomeric forms thereof.

The compounds of formula (I) may generally be prepared by cyclizing an intermediate of formula



(II)

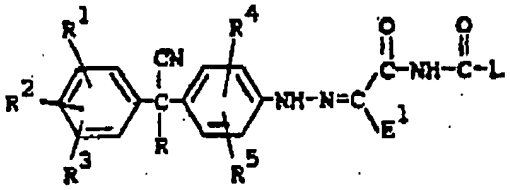
and eliminating the group E of the thus obtained dione



(III)

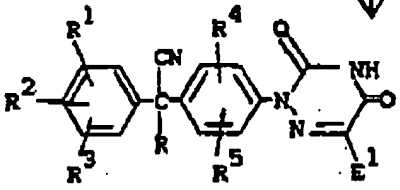
In the intermediates (II) L has the meaning of an appropriate leaving group such as C_{1-6} alkyloxy, halo and the like. The group E, as described in the intermediate (II) and the triazinedione (III), represents an appropriate electron attracting group which may conveniently be eliminated from the dione (III) such as, for example, a carboxyl, a sulfonyloxy, a sulfinyloxy group or a precursor and/or derivative thereof, e.g. an ester, an amide, a cyanide, a C_{1-6} alkylsulfonyloxy, phenylsulfonyloxy, C_{1-6} alkylphenylsulfonyloxy and halophenylsulfonyloxy and the like groups.

A particularly suitable process for preparing compounds of formula (I) consists of cyclizing an intermediate of formula (II-a) and eliminating the E^1 functionality in the thus obtained intermediate of formula (III-a). In (II-a) and (III-a) E^1 represents a cyano, C_{1-6} alkyloxycarbonyl or amide group.



(II-a)

cyclization reaction

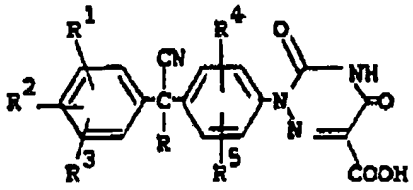


(III-a) ⟶ (I)

The cyclization reaction may be effected following art-known cyclization procedures as described, for example, in Monatshefte der Chemie, *94*, 258—262 (1963), e.g. by heating the starting compound of formula (II-a) above its melting point, or by refluxing a mixture of (II-a) with a suitable solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, methylbenzene, or dimethylbenzene, an acid, e.g. acetic acid, optionally in the presence of base, e.g. potassium acetate, sodium acetate and the like.

The elimination of the E^1 functionality may be effected following art-known procedures as described, for example, in Monatshefte der Chemie, *96*, 134—137 (1965), e.g. by converging (III-a) into a carboxylic acid (IV) in a suitable acidic reaction medium such as acetic acid, aqueous hydrochloric acid solutions or mixtures thereof. Elevated temperatures may enhance the rate of the reaction.

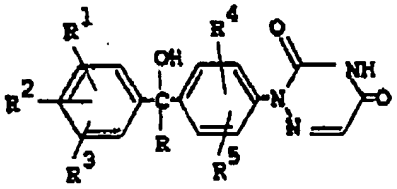
The thus obtained carboxylic acids of formula



(IV)

may be converted into a compound of formula (I) by art-known decarboxylation reaction procedures, e.g. by heating the carboxylic acid (IV) or by heating a solution of (IV) in 2-mercaptoacetic acid as described, for example, in US Patent No. 3,896,124.

The compounds of formula (I) may also generally be prepared by converting the hydroxyl function of a triazinedione of formula

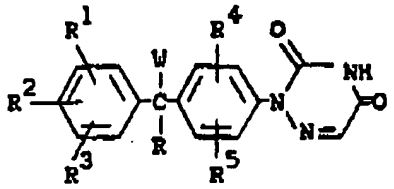


(V)

into a nitrile function.

The conversion of (V) into (I) may be effected by art-known procedures. For example, by first

converting the hydroxy function into a suitable leaving group and subsequently converting the said leaving group in the thus obtained



(VI)

into a nitrile function.

In (VI) W has the meaning of an appropriate reactive leaving group such as, for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenylsulfonyloxy.

For example, where W represents chloro, the intermediates (VI) may be prepared by reacting (V) with thionyl chloride in a suitable reaction-inert solvent.

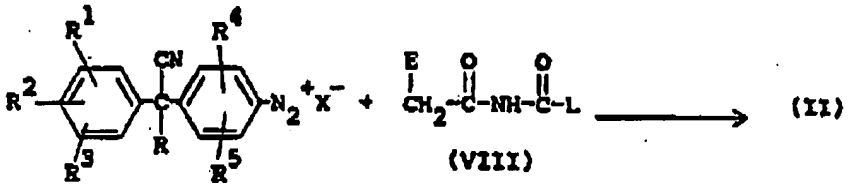
The conversion of (VI) into (I) may be effected, for example, by reacting (VI) with a cyanide, such as, for example, a alkalimetal cyanide, e.g. potassium cyanide, sodium cyanide; copper cyanide; silver cyanide and the like, if desired, in the presence of an appropriate solvent.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxy-propanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

It is obvious from formula (I) that the compounds of the present invention have an asymmetric carbon atom. Consequently, these compounds may exist under two different enantiomeric forms. Pure enantiomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures.

A number of intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds. A number of such preparation methods will be described hereinafter in more detail.

The intermediates of formula (II) may generally be prepared by reacting a diazonium salt of formula (VII) with a reagent of formula (VIII).

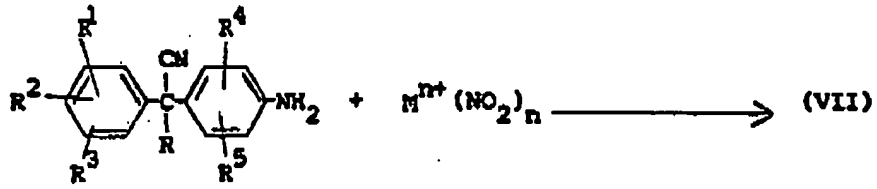


(VII) (VIII) (II)

X^-, as described in (VII) has the meaning of an appropriate anion and E and L, as described in (VII), have the previously defined meanings.

The reaction of (VII) with (VIII) may conveniently be conducted in a suitable reaction medium as described, for example, in Monatshefte der Chemie, *94*, 694—697 (1963). Suitable reaction mediums are, for example, aqueous sodium acetate solutions, pyridine and the like.

The starting diazonium salts (VII) may be derived from a corresponding amine of formula (IX) following art-known procedures by reacting the latter with an alkalimetal or earth alkaline metal nitrite, e.g. sodium nitrite, in a suitable reaction medium.



(IX) (VII)